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Brief Clinical Report

VACTERL With Hydrocephalus and Branchial Arch Defects: Prenatal, Clinical, and Autopsy Findings in Two Brothers

U.G. Froster, S.J. Wallner, E. Reusche, E. Schwinger, and H. Rehder

Departement für Frauenheilkunde, Klinik und Poliklinik für Geburtshilfe, Universitätsspital Zürich, (U.G.F.), Switzerland; Institut für Pathologie, Medizinische Universität zu Lübeck (S.J.W., E.R.), Institut für Humangenetik, Medizinische Universität zu Lübeck (E.S.), Lübeck, and Abteilung Klinische Genetik, Zentrum für Humangenetik, Philipps Universität (H.R.), Marburg, Germany

VACTERL association is defined as a combination of vertebral, anal, cardiac, tracheoesophageal, renal and limb anomalies, in particular radial defects. In recent years hydrocephalus was observed in patients with apparent VACTERL association. This particular condition was recognized as a hereditary entity with poor prognosis. Both autosomal recessive and X-linked forms were described. Here we report prenatal, clinical and autopsy findings in 2 brothers with this syndrome, who had, in addition, branchial arch anomalies. The recurrence in this family suggests X-linked inheritance. Branchial arch defects have so far not been described as part of the VACTERL + H syndrome. This observation further supports that a variety of brain anomalies including hydrocephalus associated with VACTERL anomalies represents separate entities with a considerable recurrence risk. The use of the term VACTERL "association" for these conditions is misleading and is discouraged.

KEY WORDS: VACTERL + hydrocephalus, branchial arch defects, autopsy findings, X-linked inheritance

INTRODUCTION

Brain defects occurring in association with anomalies of the VACTERL association are important criteria to suspect a distinct entity with either autosomal recessive or X-linked inheritance [Briard et al., 1984; Evans et al., 1989; Froster and Meinecke, 1992].

We report prenatal ultrasound, clinical, and autopsy findings of 2 brothers with a combination of anomalies, partly compatible with VACTERL + hydrocephalus (VACTERL + H) syndrome. These patients had, in addition, anomalies of the branchial arch and one died neonatally.

CLINICAL REPORTS

Patient 1

The male patient was the first child born to a 20-year-old mother and a 31-year-old father. The parents are healthy, and nonconsanguineous. A younger sister is healthy.

The index patient was born at term after an uneventful pregnancy. Routine ultrasound study in this pregnancy had not identified any anomalies. Birth was by cesarean section because of intrauterine hypoxia. At birth, multiple congenital anomalies were noted (Fig. 1), as summarized in Table I. The patient died at the age of 7 weeks because of cardiorespiratory distress.

On autopsy, weight was 2,440 g (<3rd centile), 46 cm length (<3rd centile), OFC 38 cm (>98th centile). Anomalies included bilateral auricular malformation with atresia of the external auditory canal, dolichocephaly, cleft of palate, hypertelorism, short palpebral fissures, prominent philtrum, thin lips, retrognathia, and a broad short neck. There was bilateral radial aplasia with only two rays but a rudimentary thumb on the right hand; anal atresia (surgically corrected after birth), malrotation of the bowel; a bronchogenic cyst of the esophagus directly above the hiatus oesophagicus of the diaphragm and incomplete lung lobation; agene-

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Address reprint requests to Dr. Ursula G. Froster, Departement für Frauenheilkunde, Klinik und Poliklinik für Geburtshilfe, Universitätsspital Zürich, Frauenklinikstr. 10 CH-8091 Zurich, Switzerland.

Fig. 1. Index patient with bilateral radial defects, microtia of the left ear.

sis of the pancreas, absence of the right kidney and a dysplastic double kidney on the left side, a subaortic ventricular septal defect with a dextroverted aorta (Eisenmenger complex), including hypertrophy of left and right ventricles. Furthermore, there was internal hydrocephalus with thinning of the cortex and partial agenesis of the corpus callosum.

Patient 2

This male fetus was the product of the third pregnancy of the same couple, 5 years after the index patient was born. In this case, prenatal ultrasound study had shown multiple defects, including bilateral radial agenesis and hydrocephalus as the major anomalies. The parents opted for termination. At birth, at 24 weeks, the male fetus weighed 430 g, length was 26 cm. He had absence of the radii with short thumbs, defects of the third ray on both hands (Fig. 2), malformed auricles with microtia on the right and atresia of the ear canal (Fig. 3). Autopsy findings included a hypoplastic pancreas, incomplete lung lobation, arteria lusoria, and agenesis of corpus callosum with hydrocephalus (Table I), without signs of Arnold-Chiari malformation. Both kidneys and the heart were normal. Chromosomes were normal (46,XY) in both cases. No chromosome breakage was found in either case.

DISCUSSION

The combination of VACTERL anomalies with hydrocephalus (VACTERL + H) was suggested to be a spe-

TABLE I. Summary of Defects in Cases With VACTERL + H Syndrome From the Literature and in the Present Cases (1 and 2)

	Author[d]																Case	
Defects[a]	1a	1b	2	3	4a	4b	5	6a	6b	6c	7a	7b	7c	7d	8*	9*	1	2
Radius defects	+	+	–	+	+	+	+	–	–	–	–	–	–	–	9/16	4/8	+	+
Humerus defects	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Preaxial ray defects	+	+	(+)	+	+	+	+	+	+	+	[b]	–	+	–		3/8	+	+
Third ray defects	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Ear dysplasia	–	–	tag	+	+	+	–	–	–	–	–	pit	–	–	+	3/8	+	+
Atretic ear canal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1/8	+	+
Cleft palate	+	+	+	–	–	–	+	–	–	–	–	–	–	–	–	2/8	+	–
Short palpebral fissure	–	–	–	(+)	–	–	–	+	–	–	–	–	–	–	–	–	+	+
Hypertelorism	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	1/8	+	+
Prominent philtrum	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Thin upper lip	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Short broad neck	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	+
Anal atresia	+	+	(+)	–	+	–	+	+	+	+	–	+	(+)	+	–	5/8	+	–
Gut malrotation	–	+	–	+	–	–	–	–	–	–	–	–	+	–	–	2/8	+	–
Esophageal anomaly	–	+	+	–	–	+	+	–	–	+	–	–	+	+	8/16	4/8	+	–
Pancreas anomaly	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Hypoplastic lung	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	1/8	+	
Absent lung lobation														+	–	4/8	+	–
Kidney anomaly	+	+	+	+	+	+	+	+	+	+	+	–	+	+	10/16	7/8	+	–
Heart defect	–	–	+	–	–	–	+	+	+	+	+	–	+	+	6/16	6/8	+	–
Hydrocephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16	8/8	+	+
Microphthalmia	–	–	–	–	+	+	–	–	–	–	–	+	–	–	2/16	3/8	+	+
Large head	–	–	+	–	+	–	–	+	+	+	+	+	+	(+)	–	3/8	+	+
Vertebral defects	–	–	+	–	–	+	+	+	+	+	+	+	+	+	9/16	2/8	+	–
Other		1	2	3		4	5	6	7				8					
Sex	m	m	m	m	m	m	m	m	m	f	m	m	f	f	8m 8f	2m 6f	m	m
Inheritance	XR[c]	XR	XR	XR	Sp[c]	Sp	Sp	AR[c]	Sp	Sp	Sp	Sp	Sp	Sp			XR	XR

[a]Other additional anomalies: small head; chromosomal breaks; small head, absent cerebellum, accessory spleen; sacral agenesis; occipital encephalocele; meningocele, retrourethral fistula; sacral defects; retrovaginal fistula.
[b]Preaxial polydactyly.
[c]Sp, sporadic case; AR, autosomal recessive; XR, X-linked.
[d]Authors: 1, Genuardi et al. [1993]; 2, Evans and Chodiker [1993]; 3, Kunze et al. [1992]; 4, Porteous et al. [1992]; Corsello and Giuffre [1994]; 6, Iafolla et al. [1991]; 7, Vandenborne et al. [1993]; 8, Briard et al. [1984] (*16 cases); 9, Evans et al. [1989] (*8 cases).

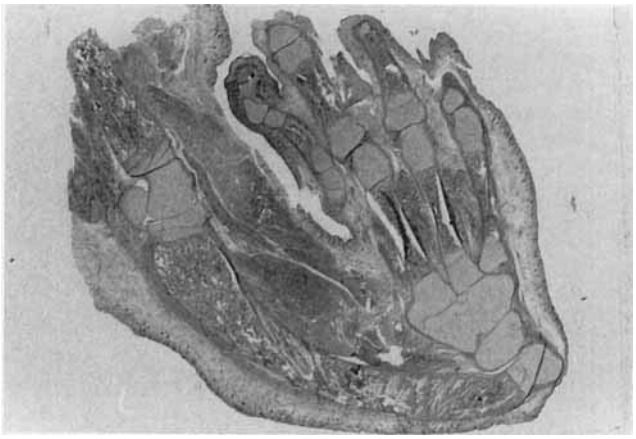

Fig. 2. Histology of the left hand, showing defect of the third ray and radius deficiency (H and E stain).

cific entity with either autosomal recessive or X-linked inheritance [Evans et al., 1989]. Excess chromosome breakage was reported in some cases, suggesting a severe form of Fanconi syndrome [Sommer et al., 1989; Porteous et al., 1992]. Increased rates of chromosome breakage and rearrangements were also present in some X-linked cases with hydrocephalus secondary to Arnold-Chiari malformation [Wang et al., 1993], but do not appear to be a constant or clearly distinguishing finding in this syndrome. Prognosis for survival in most cases with VACTERL + H was poor and only few patients have survived, most of them with considerable developmental and physical handicap [Iafolla et al., 1991; Evans and Chodirker, 1993].

The clinical differentiation between autosomal recessive and X-linked cases of this condition is difficult. It appears that criteria suggesting X-linked inheritance include hydrocephalus caused by Arnold-Chiari malformation, cleft palate and microphthalmia. The patients reported here do not have Arnold-Chiari malformation. However, they do have anomalies of the branchial arch with microtia and atretic ear canal occurring as a constant manifestation. These abnormalities, representing branchial arch defects, have so far not been reported as components of the VACTERL + H syndrome, even though malformed ears, ear tags and ear pits were mentioned occasionally [Evans and Chodirker, 1993; Kunze et al., 1992; Porteous et al., 1992; Vandenborne et al., 1993]. The clinical features reported here show some overlap with an MCA syndrome including encephalocele, radial defects, cardiac, gastrointestinal and renal anomalies observed in two sporadic female cases [Froster and Meinecke, 1992]. However, these patients did not have branchial arch defects. Another possibly distinguishing characteristic might be the defect of the third ray of the hand, which was only identifiable after specific histological investigations (Fig. 2). This might represent a form of split-hand malformation. Anomalies of the brain, the first branchial arch, and microphthalmia as observed in the family described here, suggest a primary defect of neural crest development in this heritable condition. The term "VACTERL" appears misleading for these complex syndromes, in particular with respect to genetic counselling. Even though there is some reluctance in using eponymic terms for syndromes, the term "Briard-Evans-syndrome" might be preferable to using "VACTERL-H syndrome" in order to avoid confusion. For practical counselling purposes, any patient with additional anomalies exceeding the spectrum of VACTERL association has to be considered as presenting an hereditable condition and prenatal ultrasound study should be offered in future pregnancies.

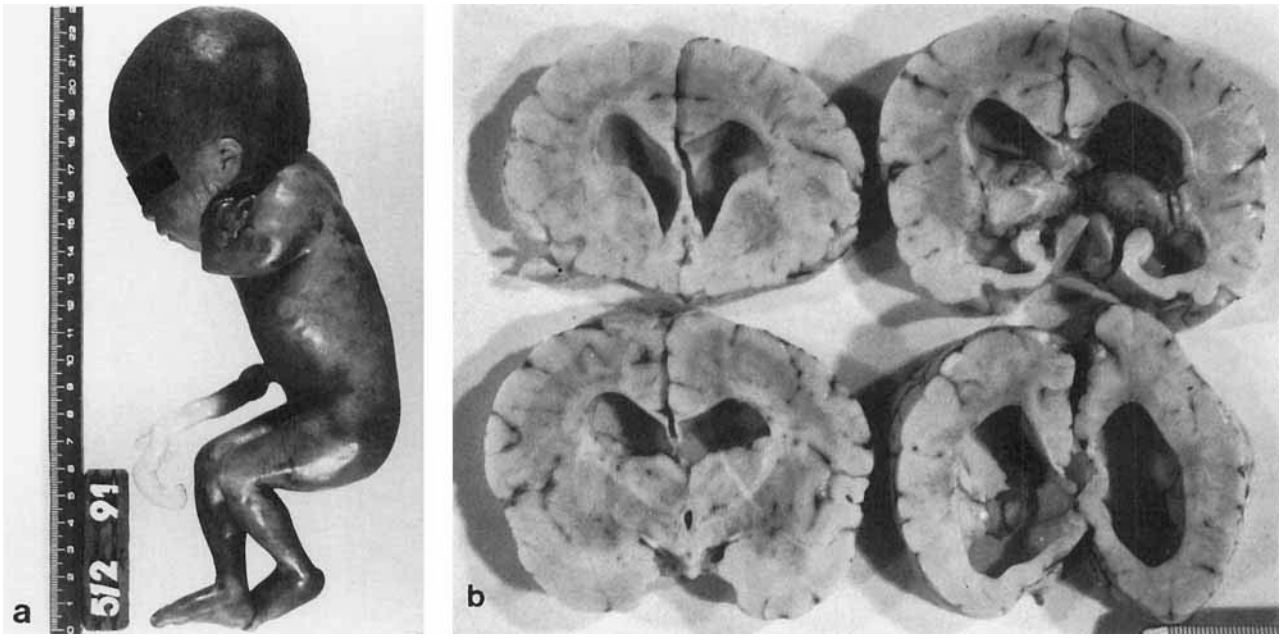

Fig. 3. **a:** External aspect of case 2; note radial defect, small ear on the left side. **b:** Brain defect, showing internal hydrocephalus with fusion defects of the corpus callosum and septum pellucidum.

Further evaluation of such cases, including complete autopsy reports, are necessary to decide whether clinical differences are sufficient to distinguish between X-linked and autosomal-recessive cases within this subgroup of syndromes. Defects of the branchial arch and third ray defects of the hand might be such distinguishing signs.

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